Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Resistance to anti-influenza agents

Published online
September 22, 2005
DOI:10.1016/S0140-6736(05)
67340-0

See **Articles**
pages 1165 and 1175

The current heightened state of awareness about the pandemic potential of H5N1 avian influenza viruses in southeast Asia should not detract from the fact that human influenza viruses continue to cause a substantial burden of disease. More than half a million people are estimated to die from influenza-associated complications every year.[1] As with many infectious agents, control of influenza virus infection is sought in two main ways: prevention, either by vaccination or drug prophylaxis, and treatment with antiviral drugs.

Although vaccines can reduce infections, influenza viruses are prone to a high rate of antigenic change in the haemagglutinin and neuraminidase surface glycoproteins, evolving rapidly to evade recognition by the adaptive immune system of the host.[2] Vaccine designers of the WHO Global Influenza Programme are therefore forced to prepare new antigenic formulations every year, predicting likely candidate virus targets up to 9 months in advance, with no guarantee of a perfect match between vaccines and circulating strains. An important target group for vaccination is elderly people, who are at high risk of developing complications after influenza infection. In today's *Lancet*, Tom Jefferson and co-workers[3] describe their meta-analysis combining vaccine trials and cohort and case-control studies in people older than 65 years. Hampered by variations in the conditions, design, and quality of the studies assessed, the authors nonetheless show that vaccination seems to have a modest effect in reducing influenza-related complications, although little efficacy in preventing initial symptoms. Jefferson and colleagues' findings suggest that improvements in vaccine coverage and formulations could further reduce initial influenza infections. While designers of vaccines targeting emerging pandemic strains of avian H5N1 influenza have a special challenge, in that the pandemic strain is not yet apparent and may appear with little warning, strategic vaccination coverage will be important to reduce infection and complications in at-risk groups.

Currently available anti-influenza drugs (table) include the adamantines, amantadine and rimantadine, which target the viral M2 ion-channel protein, and the neuraminidase inhibitors oseltamivir and zanamivir.[4] These antiviral drugs are widely used,[5] particularly the older amantadine, which in some countries is available over the counter in "anti-flu" formulations. Drugs are an important component of plans for influenza containment, and stockpiling of both classes of drug has been advocated. A study by Rick Bright and colleagues,[6] also in today's *Lancet*, points to a potential major caveat for this plan: the emerging problem of resistance to antiviral drugs. In this instance, resistance to adamantines in prevailing human H3N2 influenza viruses is the focus; however, the findings are also relevant to control measures for avian H5N1 influenza.

Bright and colleagues' genotypic study shows a dramatic increase in the prevalence of amantadine-resistant H3N2 strains in some southeastern Asian countries, which has contributed to an increase of more than 30-fold in the frequency of worldwide viral resistance between 1994–95 and 2003–04. It seems that complacency had arisen from the low frequency of resistance observed in previous studies, and the importance of surveillance for the emergence and spread of resistant strains was given low priority. In the midst of increased vigilance towards emerging avian H5N1 viruses, Bright's human influenza study serves as a timely reminder to watch this family of old foes closely. In view of the practical implications, the H3N2 amantadine-resistance study will be of great interest to those who have been involved in epidemic and pandemic preparedness and should encourage them to consider upgrading levels of surveillance.

Although the mechanism for generation of adamantine resistance has not been fully elucidated, it might be associated with inappropriate drug administration. The adamantines rapidly induce resistance; resistant virus can be detected after just 3 days of treatment. Thus the wide use, and sometimes loose control, of

	Year of approval (US FDA)	Availability	Daily dose†	Resistance (in treated human beings)[4,5]
Amantadine	1966	Prescription*	2×100 mg	Regularly detected
Rimantadine	1993	Prescription*	2×100 mg	Regularly detected
Zanamivir	1999	Prescription	2×10 mg	Rarely detected
Oseltamivir	1999	Prescription	2×75 mg	Rarely detected

FDA=Food and Drug Administration. *Amantadine and rimantadine are available over the counter in some countries. †US Centers for Disease Control and Prevention suggested daily dose for treatment of influenza A in adults (age 13–64 years).

Table: **Currently available antivirals for use against influenza**

amantadine could be to blame. Amantadine is a prescription drug in most countries, but is readily available over the counter in Russia, China, and perhaps other countries, where it may be consumed either knowingly or unknowingly at non-optimal doses. The recent outbreak of severe acute respiratory syndrome (SARS) might have contributed to the 2003 "spike" in adamantine resistance, which was most prominent in China and Hong Kong. During the outbreak, demand for antivirals, even those inappropriate for treatment of SARS, is likely to have increased. This kind of overreaction might also be observed should an H5N1 avian influenza outbreak occur.

The origin of amantadine-resistant H5N1 variants in Vietnam and neighbouring regions is still unclear. One possible explanation for the emergence of adamantine-resistant virus could be the alleged administration of the drug in agricultural practices in southeast Asia, in poultry farming in particular. However, this allegation has not been verified and is strongly denied by some governments.[7] Naturally occurring resistance-associated mutations could also have arisen. Bright and co-workers observed that only two of 92 US patients shedding resistant H3N2 virus had a documented history of antiviral treatment before collection of virus. How the viruses affecting the remaining patients gained resistance remains open to conjecture. This relatively high frequency of resistance of unknown origin in patients raises the possibility that the resistant Asian viruses observed in Bright's study may not have arisen solely as a result of exposure to drugs.

Is drug resistance now the norm? Assuming that distribution and administration of adamantines is controlled, we predict that the "spike" of resistance to adamantine found in Bright's study may wane over the next 2–3 years, perhaps due to continued viral evolution or, probably, competitive disadvantage of resistant virus. To ensure that resistance does subside, surveillance should be used as an active, rather than a passive, method to track the frequency of resistant viruses in real time, and not retrospectively. However, continued uncontrolled use of adamantines might prevent the natural passing of this aberration, and continued misuse of drugs could cause resistant viruses to linger.

The studies published today reinforce the shortcomings of our efforts to control influenza. For too long, the development and manufacture of influenza vaccines and antiviral drugs has been of limited interest to drug companies. Since the existing defences are limited, it is critical that the most is made of them. Thus, although increasing resistance to adamantine is a cause for concern, it is still too early to call for market withdrawal or exclusion from stockpiling. What is needed is to improve control over the distribution and availability of the adamantine drugs, particularly in developing and southeast Asian countries, and to increase surveillance for resistance, so that these cheap and easily administered drugs can continue to play a part in our influenza control strategies. No one class of drug can be relied on: the newer neuraminidase inhibitors are also facing resistance issues,[8] and despite their sometimes prohibitive expense, distribution should also be controlled. A wide-ranging approach must be taken to prevent and control endemic, epidemic, and pandemic influenza infection, with an emphasis on increased surveillance, better management of our existing tools of vaccination, M2 ion-channel blockers, and neuraminidase inhibitors, and the development of new agents to boost our arsenal.

*Yi Guan, Honglin Chen
Joint Influenza Research Centre (SUMC & HKU), Shantou University Medical College, Shantou, Guangdong 515031, China, (YG, HC); and Department of Microbiology and State Key Laboratory for Emerging Infectious Diseases, University of Hong Kong, Faculty of Medicine Building, Pokfulam, Hong Kong Special Administrative Region, China (YG, HC)
yguan@hkucc.hku.hk

We declare that we have no conflict of interest.

1 Schmidt AC. Antiviral therapy for influenza: a clinical and economic comparative review. *Drugs* 2004; **64:** 2031–46.
2 Hilleman MR. Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. *Vaccine* 2002; **20:** 3068–87.
3 Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet* 2005; **366:** 1165–74.
4 Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. *Lancet* 2000; **355:** 827–35.
5 Suzuki H, Saito R, Masuda H, Oshitani H, Sato M, Sato I. Emergence of amantadine-resistant influenza A viruses: epidemiological study. *J Infect Chemother* 2003; **9:** 195–200.
6 Bright RA, Medina M-j, Xu XY, et al. Incidence of adamantine resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005; **366:** 1175–81.
7 Cyranoski D. China's chicken farmers under fire for antiviral abuse. *Nature* 2005, **435:** 1009.
8 Neuraminidase Inhibitor Susceptibility Network. Use of influenza antivirals during 2003–2004 and monitoring of neuraminidase inhibitor resistance. *Wkly Epidemiol Rec* 2005; **80:** 156.